NDA 9-000/S-013/S-015/S-017/S-020/021 OCT 31 2000

Novartis Pharmaceuticals Corporation
Attention: Kay A. Chitale, Pharm.D.
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Dr. Chitale:

Please refer to your supplemental new drug applications dated February 16, 1990 (S-013), November 12, 1990 (S-015), December 5, 1991 (S-017), August 16, 1993 (S-020), and November 14, 1996 (S-021), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cafergot (ergotamine tartrate and caffeine, USP) Suppositories.

These supplemental new drug applications provide for the following revisions to product labeling:

9-000/S-013

1. Revised storage instructions under the HOW SUPPLIED section to reduce the recommended storage temperature from 86°F (30°C) to 77°F (25°C) in order to provide increased assurance that the drug will have the purity characteristics it is represented to possess.
2. The addition of the established name after the tradename wherever it appears throughout the labeling.
3. Alphabetization of the inactive ingredients under the DESCRIPTION section of labeling.
4. The addition of the NDC codes for the drug product packages under the HOW SUPPLIED section.

9-000/S-015

This supplement provides for the removal of all references to the Cafergot P-B tablets and suppositories since Novartis (formerly Sandoz) discontinued marketing these products.

9-000/S-017

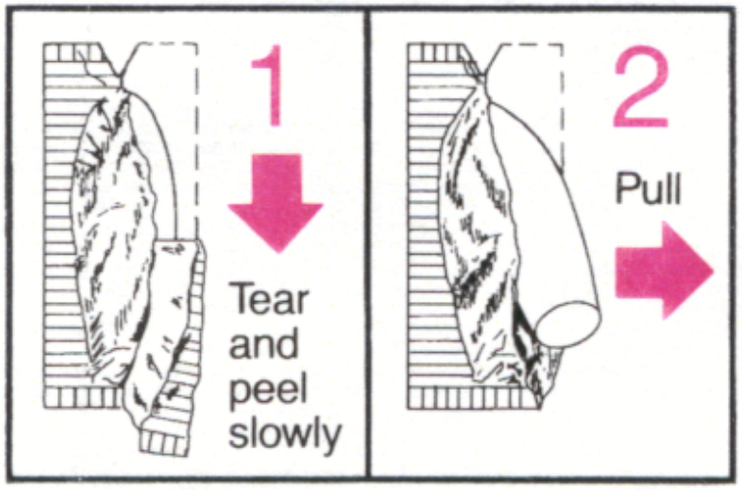
1. The addition of safety information in the CONTRAINDICATIONS, PRECAUTIONS, INFORMATION FOR PATIENTS, DRUG INTERACTIONS, DRUG ABUSE and DEPENDENCE, and OVERDOSAGE sections of labeling.
2. The addition of Pregnancy, Nonteratogenic Effects, Labor and Delivery, Nursing Mothers, and Pediatric Use sections under the PRECAUTIONS section of labeling.
3. The addition of safety information regarding rare cases of solitary rectal or anal ulcer which occurred from abuse of ergotamine derivatives in the PRECAUTIONS-General section of labeling.

APPROVED

--------- ℞ label -------

OCT 31 2000

OPENING INSTRUCTIONS:
Avoid excessive handling of suppository which is designed to melt at body temperature. If soft, chill in refrigerator or freezer before opening foil wrapper.



SigPak® (dispensing unit) package

CAFERGOT® suppository

(ergotamine tartrate and caffeine) suppositories, USP

Store and Dispense: Below 77°F (25°C); tight container (sealed foil).
IF SOFT, CHILL IN REFRIGERATOR BEFORE OPENING FOIL WRAPPER

N 3 0078-0033-02 2

SigPak® *(dispensing unit) package*

NEW COLOR FOIL

NDC 0078-0033-02

CAFERGOT®

(ergotamine tartrate and caffeine) suppositories, USP

suppository

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PHARMACEUTICALS
CORPORATION
EAST HANOVER, NJ 07936

Points to Remember

1. Please give this package to the pharmacist when refilling this prescription. The package has your prescription number on the pharmacy label.

2. This factory sealed SigPak® package is a convenient way to carry or store Cafergot Suppositories.

3. If a suppository becomes soft, chill in refrigerator before opening the foil wrapper. The foil wrapper helps to assure the purity, quality and potency of the medication.

4. Cafergot suppositories are for rectal use only.

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CAFERGOT® is a registered trademark of Sandoz Pharmaceuticals Corporation, a company which has been researching & producing medicines for headache for over 40 years.

10513103

SigPak®
(dispensing unit) package

12 SUPPOSITORIES

NDC 0078-0033-02

6505-01-140-2707

CAFERGOT® suppository

(ergotamine tartrate and caffeine) suppositories, USP

EACH SUPPOSITORY CONTAINS:
ergotamine tartrate USP ..... 2 mg
caffeine USP ..... 100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

USUAL ADULT DOSE:
For dosage, see product information attached.

CAUTION:
Federal law prohibits dispensing without prescription.

Store and Dispense:
Below 77°F (25°C); tight container (sealed foil).

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10513103

CAFERGOT®

30613903

(ergotamine tartrate and caffeine) SUPPOSITORIES, USP

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

CAFERGOT® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP ..... 2 mg
caffeine USP ..... 100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

CAFERGOT® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage. If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

CLINICAL PHARMACOLOGY

Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

INDICATIONS AND USAGE

CAFERGOT® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS

CAFERGOT® (ergotamine tartrate and caffeine) may cause fetal harm when administered to pregnant women. CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus.

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis.

Hypersensitivity to any of the components.

PRECAUTIONS

General

Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the rectally administered drug, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

Rare cases of a solitary rectal or anal ulcer have occurred from abuse of ergotamine suppositories usually in higher than recommended doses or with continual use at the recommended dose for many years. Spontaneous healing occurs within usually 4-8 weeks after drug withdrawal.

Information for Patients

Patients should be advised that one suppository of CAFERGOT® (ergotamine tartrate and caffeine) should be taken at the first sign of a migraine headache. No more than 2 suppositories should be taken for any single migraine attack. No more than 5 suppositories should be taken during any 7-day period. CAFERGOT® (ergotamine tartrate and caffeine) should be used only for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties. Patients should be advised to report to the physician immediately any of the following: numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, swelling or itching.

Drug Interactions

CAFERGOT® (ergotamine tartrate and caffeine) should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker Inderal (propranolol) has been reported to potentiate the vasoconstrictive action of CAFERGOT® (ergotamine tartrate and caffeine) by blocking the vasodilating property of epinephrine. Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

The blood levels of ergotamine-containing drugs are reported to be elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported with therapeutic doses of the ergotamine-containing drugs when coadministered with these antibiotics.

Pregnancy

Teratogenic Effects

Pregnancy Category X: There are no studies on the placental transfer or teratogenicity of the combined products of CAFERGOT® (ergotamine tartrate and caffeine). Caffeine is known to cross the placenta and has been shown to be teratogenic in animals. Ergotamine crosses the placenta in small amounts, although it does not appear to be embryotoxic in this quantity. However, prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone leading to reduced myometrial and placental blood flow may have contributed to fetal growth retardation observed in animals. *(See CONTRAINDICATIONS)*

Nonteratogenic Effects

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in pregnancy due to the oxytocic effects of ergotamine. *(See CONTRAINDICATIONS)*

Labor and Delivery

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in labor and delivery due to its oxytocic effect which is maximal in the third trimester. *(See CONTRAINDICATIONS)*

Nursing Mothers

Ergot drugs are known to inhibit prolactin but there are no reports of decreased lactation with CAFERGOT® (ergotamine tartrate and caffeine). Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Because of the potential for serious adverse reactions in nursing infants from CAFERGOT® (ergotamine tartrate and caffeine), a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular: Vasoconstrictive complications of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, EKG changes and muscle pains. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other cardiovascular adverse effects include transient tachycardia or bradycardia and hypertension.

Gastrointestinal: Nausea and vomiting; rectal or anal ulcer (from overuse of suppositories).

Neurological: paresthesias, numbness, weakness, and vertigo.

Allergic: Localized edema and itching.

Fibrotic Complications: There have been a few reports of patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy developing retroperitoneal and/or pleuropulmonary fibroses. There have also been rare reports of fibrotic thickening of the aortic, mitral, tricuspid, and/or pulmonary valves with long-term, continuous use of CAFERGOT® (ergotamine tartrate and caffeine).

DRUG ABUSE AND DEPENDENCE

There have been reports of drug abuse and psychological dependence in patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism. *(See PRECAUTIONS)*

OVERDOSAGE

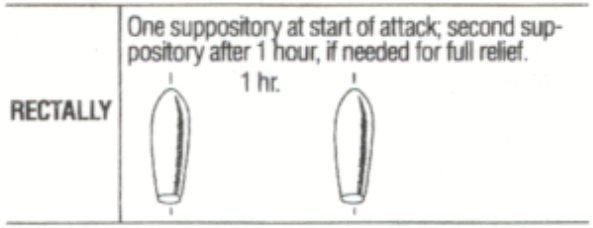
The toxic effects of an acute overdosage of CAFERGOT® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by enema. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions and blood pressure are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be beneficial but caution must be exercised to avoid aggravating an already existent hypotension.

DOSAGE AND ADMINISTRATION

Procedure

For the best results, dosage should start at the first sign of an attack.



Early Administration Gives Maximum Effectiveness

Maximum Adult Dosage

Rectally

Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 5 suppositories.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

HOW SUPPLIED

CAFERGOT® (ergotamine tartrate and caffeine) Suppositories, USP

Yellowish-white bullet-shaped, cocoa butter base suppositories wrapped in silver colored foil with

" CAFERGOT® SUPPOSITORY 78-33 SANDOZ" printed in fuchsia.

Boxes of 12 (NDC 0078-0033-02).

Store and Dispense

Below 77°F (25°C); tight container (sealed foil).

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Before dispensing, tear off this portion at perforation.